

Staging of Regional Nodes in AJCC Stage I and II Melanoma: ¹⁸F-FDG PET Imaging versus Sentinel Node Detection

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ABSTRACT

Primary Purpose. The staging of regional nodes by means of sentinel node detection has been shown to accurately detect subclinical nodal metastases from cutaneous melanoma. On the other hand, the oncological applications of ¹⁸F-fluoro-2-deoxy-D-glucose positron emission tomography (¹⁸F-FDG PET) are, nowadays, firmly established. However, the sensitivity of such metabolic imaging for staging the regional nodes in primary melanoma remains debatable. We prospectively assessed the actual value of PET for detecting sentinel node metastases in 21 consecutive patients presenting with early-stage melanoma.

Materials and Methods. Twenty-one melanoma patients scheduled for lymphatic mapping and sentinel lymphadenectomy underwent fully corrected whole-body PET using ¹⁸F-FDG. In all cases, the disease was initially classified as either stage I or II, from the latest version of the American Joint Committee on Cancer staging system. The sentinel node detection was systematically performed within the week following the PET scan. Serial sections of the sentinel nodes were analyzed by both conventional pathology and immunohistochemical staining. Metastatic sentinel nodes were also assessed for the size of tumor

deposits and the degree of nodal involvement (focal, partial, or massive). The median follow-up time was 12 months.

Results. Six of the 21 patients (28.5%) had an involved sentinel node. PET was positive in only one case with a sentinel node >1 cm. In the five other cases, the sentinel nodes missed by PET were <1 cm with focal and/or partial involvements. One patient, free of regional nodal metastases in both sentinel node detection and PET imaging, had, however, a same-basin recurrence 3 months later. In another case, PET had one false positive result. Overall, the sentinel detection of subclinical nodal metastases had a sensitivity of 86%. PET detected only 14% of sentinel node metastases.

Conclusions. Sentinel node detection remains the procedure of choice for detecting subclinical lymph node involvement from primary cutaneous melanoma. Owing to its limited spatial resolution, PET appears insufficiently sensitive to identify microscopic nodal metastases. As a practical consequence, metabolic imaging is not recommended as a first-line imaging strategy for staging regional lymph nodes in patients with stage I or II melanoma. *The Oncologist* 2002;7:271-278

INTRODUCTION

Malignant melanoma of the skin remains a critical public health problem worldwide despite earlier diagnosis due to screening and public education [1]. As melanoma cells primarily spread through the lymphatic way, the N classification

of such lymphophilic cancer is a key step for treatment planning and patient prognosis [2, 3].

According to the sentinel node theory, the disease progresses in an orderly fashion, and thus, affects the regional nodes draining the primary tumor before disseminating to

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distant sites [4, 5]. Subsequently, the lymphatic mapping followed by sentinel lymphadenectomy (LM/SL) has become a valuable tool for detecting subclinical lymph node metastases from melanoma [6-8]. Though even the therapeutic benefit of complete selective lymph node dissection (CSLND) has not yet been proven, the clinical usefulness of LM/SL in terms of staging accuracy and prognostic significance is widely recognized nowadays [7, 9, 10].

On the other hand, the utility of a sophisticated metabolic imaging technology, such as positron emission tomography (PET) using ^{18}F -fluoro-2-deoxy-D-glucose (^{18}FDG) for staging various malignancies, is firmly established. Many published data report the capability of ^{18}FDG PET in detecting lymph node involvement missed by morphological imaging procedures. Indeed, ^{18}FDG PET has been shown to localize metastatic deposits in normal-sized nodes [11-14]. Nonetheless, in pretreatment nodal staging of malignant melanoma, the actual value of PET imaging is debatable. While initial reports emphasized the high sensitivity of PET for detecting impalpable metastatic nodes [15-19], more recent studies underlined its low efficiency for diagnosing microscopic nodal involvement [20-24]. For this purpose, we prospectively evaluated the contribution of metabolic imaging for detecting sentinel node metastases in 21 consecutive patients presenting with early-stage primary melanoma, which underwent both ^{18}FDG PET imaging and LM/SL.

MATERIALS AND METHODS

Patient Population

Twenty-one consecutive melanoma patients (10 men, 11 women, mean age = 58 ± 11 years, Breslow's thickness = 1.89 mm) scheduled for a LM/SL underwent ^{18}FDG PET imaging in pretreatment staging. All patients included into this institutional protocol were classified at stage I or II cutaneous melanoma (T1-4 N0 M0) according to the latest version of the American Joint Committee on Cancer (AJCC) staging system [25]. The patients with histologically unproven primary melanoma or those with confirmed but more advanced disease (AJCC stages III or IV), as well as subjects previously treated for malignant melanoma or other malignancies were systematically excluded from the study group. Additionally, in our staging protocol, only the patients who underwent LM/SL within the week following the metabolic imaging were taken into account. The LM/SL technique included, in a 1-day protocol, a preoperative lymphoscintigraphy followed by an intraoperative lymphatic mapping using gamma probe guidance. Each patient was individually followed with a median follow-up time of 12 months. Post-therapy surveillance included complete physical examination at the control visits and oriented imaging

procedures, such as computed tomography or PET, when clinically indicated. All cases were managed by a multidisciplinary melanoma group study including a surgeon, a dermatologist, a nuclear physician, a pathologist, and an oncologist. Patient characteristics are detailed in Table 1.

PET Imaging Procedure

All patients underwent fully corrected whole-body PET imaging using either a PENN PET 240H scanner (UGM; Philadelphia, PA), in 13 cases, or a C-PET scanner (Adac, Philips Medical Systems; Milpitas, CA) in eight patients. The spatial resolution of these scanners in clinical practice approaches 1 cm. Patients fasted at least 4 hours before injection time to reduce serum glucose and insulin levels to near basal concentrations. Intravenous injection of diuretics (furosemide, 10 mg) was performed to avoid bladder and ureter artifacts. In addition, the patients received 10 mg of diazepam orally about 1 hour prior to starting the study in order to provide muscle relaxation. Patients were kept at rest and were asked to void just before starting the acquisition. PET scans were performed 60 to 90 minutes after i.v. injection of 259 to 333 MBq of ^{18}FDG . Scanning started at the inguinal region and proceeded to the neck. Optional views were focused over the neck, the groin, or the popliteal fossa in order to verify all physiological nodal stations potentially draining the primary tumor. In all cases, a whole-body segmented attenuation correction was performed post-injection using singles transmission scans with a $^{137}\text{Cesium}$ external point source. The total scanning time was, on average, 60 minutes. The data were reconstructed by using an iterative method based on an ordered subset-expectation maximization algorithm. UGM software was used for data acquisition and processing. Finally, the images were displayed on transversal, coronal, and sagittal slices and were visually interpreted in routine clinical fashion.

LM/SL Procedure

Preoperative Lymphoscintigraphy

A mean activity of 37 MBq (1 mCi) of $^{99\text{m}}\text{Tc}$ -ultrafiltered sulfur-colloid (Lymphoscint[®], Nycomed Amersham Sorin[®]; Milan, Italy; mean size = 50 nm) divided into four insulin syringes (23-gauge) was injected intradermally (0.1 to 0.15 cc per syringe) in two to four points around the primary site. Massage and compression of the sites of injection for 1 to 2 minutes were applied to stimulate the lymphatic flow. Dynamic sequences followed by static spot views over the lymphatic basins were performed using a DSX rectangular gamma camera (Sopha Medical; GE Medical Systems Benelux, Diegem, Belgium). A $^{57}\text{Cobalt}$ flood was also placed under the gamma camera performing a virtual transmission in

Table 1. Patient characteristics

| Patient <i>n</i> | Age (year) | Gender | Primary tumor sites | Breslow's depth (mm) | Clark's level | AJCC Stage |
|---------------------|---------------|--------|------------------------|-------------------------|---------------|---------------|
| 1 | 52 | M | Head and neck | 2.4 | IV | II |
| 2 | 62 | M | Head and neck | 3.6 | IV | II |
| 3 | 46 | F | Lower extremity | 0.6 | II | Ia |
| 4 | 49 | F | Trunk | 2.8 | IV | II |
| 5 | 49 | M | Lower extremity | 1.7 | IV | Ib |
| 6 | 39 | F | Trunk | 0.56 | III | Ia |
| 7 | 65 | F | Lower extremity | 4.25 | V | II |
| 8 | 58 | F | Trunk | 1.33 | IV | Ib |
| 9 | 66 | M | Trunk | 1.4 | IV | Ib |
| 10 | 76 | M | Upper extremity | 3.85 | IV | II |
| 11 | 44 | F | Upper extremity | 0.5 | I | Ia |
| 12 | 50 | F | Trunk | 1.3 | IV | II |
| 13 | 78 | M | Upper extremity | 0.7 | III | Ia |
| 14 | 48 | F | Upper extremity | 2.1 | IV | II |
| 15 | 50 | M | Upper extremity | 1.18 | IV | Ib |
| 16 | 74 | M | Trunk | 1.1 | IV | Ib |
| 17 | 77 | F | Upper extremity | 1.6 | IV | Ib |
| 18 | 73 | F | Head and neck | 4.56 | V | II |
| 19 | 48 | M | Lower extremity | 2.35 | IV | II |
| 20 | 63 | F | Lower extremity | 0.73 | IV | Ia |
| 21 | 59 | M | Trunk | 1.4 | IV | Ib |

Abbreviation: AJCC = American Joint Committee on Cancer (Last version 2001).

order to define the body contours, and thus, to localize more accurately the site of the sentinel lymph nodes (SLNs). For the axillary areas, optional views were acquired mimicking the surgical position of the patients. According to the standard definition, the first lymph node identified on the initial scans and confirmed on at least two static images was considered as the SLN [8]. The skin covering the SLN was tattooed to guide the surgical excision.

Intraoperative Gamma Probe Guidance

Three to four hours after the preoperative lymphoscintigraphy, the patients were referred to the operating room. Intraoperative lymphatic mapping was performed by using a hand-held gamma probe (Navigator[®] using a CdTe detector; Autosuture[®], Tyco Healthcare; Mechelen, Belgium). Radioactivity (in counts/sec) of the SLNs and the adjacent non-SLNs was measured *in vivo* and verified *ex vivo* after removal. A signal to background ratio higher than 2 to 3 *in vivo* and higher than 10 *ex vivo* was considered significant. After excision of the SLNs, the lymphatic basin was rechecked for radioactivity. The use of blue dye was left at the discretion of the surgeon. In all cases, the LM/SL procedure was performed by the same surgical team.

Histologic Analysis of the SLNs

Serial sections of the SLNs were examined by the same pathologist using, in all cases, both conventional pathology (hematoxylin and eosin) and immunohistochemical stains with antibodies to S-100 protein, HMB-45, and NKIC3 antigens. In cases of involved SLNs, the tumor deposits were microscopically measured and the lymph node involvement was described as massive, partial, or focal following the degree of lymph node invasion.

Statistical Analysis

The results of ¹⁸F-FDG PET and LM/SL were expressed in terms of sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values, respectively. Estimates are presented with a 95% confidence interval (95% CI). Any hypermetabolic focus detected by PET in the lymphatic basin draining the primary tumor was considered as true positive when the result matched with an SLN histologically involved. Otherwise, all hypermetabolic foci not confirmed by the histology or corresponding to inflammatory nodes were interpreted as false positive results. A negative PET scan matching with an SLN histologically free of tumor was considered as true negative. Conversely, the result of PET was considered as

falsely negative when the SLN detected by LM/SL was histologically involved. The same-basin recurrences were also considered as false negative results of PET and/or LM/SL when the initial interpretation did not conclude to a nodal involvement.

RESULTS

In the present series, 6 of the 21 melanoma patients (28.5%) had an involved SLN, which was easily localized in both preoperative and intraoperative detection. PET was positive in only one patient, who had a metastatic SLN measuring 1.8 cm with massive involvement and capsular infiltration (Fig. 1). This patient was clinically classified at AJCC stage II disease at the time of the PET scan and had progressed to AJCC stage IV melanoma after the diagnosis of microscopic lung metastases on a thoracic computed tomography. In the five other cases, the positive SLNs missed by the metabolic imaging were <1 cm, and most often harbored microscopic and focal tumor deposits (Fig. 2). Two of these (2/5) were only detected by using immunohistochemical stains. Another patient with AJCC stage I disease had a confirmed same-basin recurrence 3 months after intervention, while both LM/SL and PET were initially negative. In addition, PET had one false positive result and 13 true negatives (SLNs free of tumor and no subsequent recurrence) with a median follow-up of 12

months. The patients having a positive SLN underwent CSLND followed by high-dose systemic adjuvant interferon α -2B according to the scheme of *Kirkwood et al.* [26]. Otherwise, the patients with negative SLNs had no subsequent treatments and were clinically followed up at the control visits.

Overall, in pretreatment staging of subclinical melanoma nodal metastases, LM/SL had an 86% sensitivity, a 100% specificity, a 95% diagnostic accuracy, a 100% positive predictive value, and a 93% negative predictive value. For detecting SLN metastases, PET had a 14% sensitivity, a 93% specificity, a 67% diagnostic accuracy, a 50% positive predictive value, and a 68% negative predictive value. The performances of each procedure with their 95% confidence intervals are summarized in Table 2.

DISCUSSION

In melanoma patients presenting with AJCC stage I or II disease, the histological status of the regional lymph nodes is the most important prognostic factor [27]. This explains why it is crucial to achieve an accurate nodal staging in patients at risk of metastases. Such a need is even more warranted by the survival benefit obtained in patients with nodal involvement treated by high-dose systemic adjuvant interferon α -2B [26].

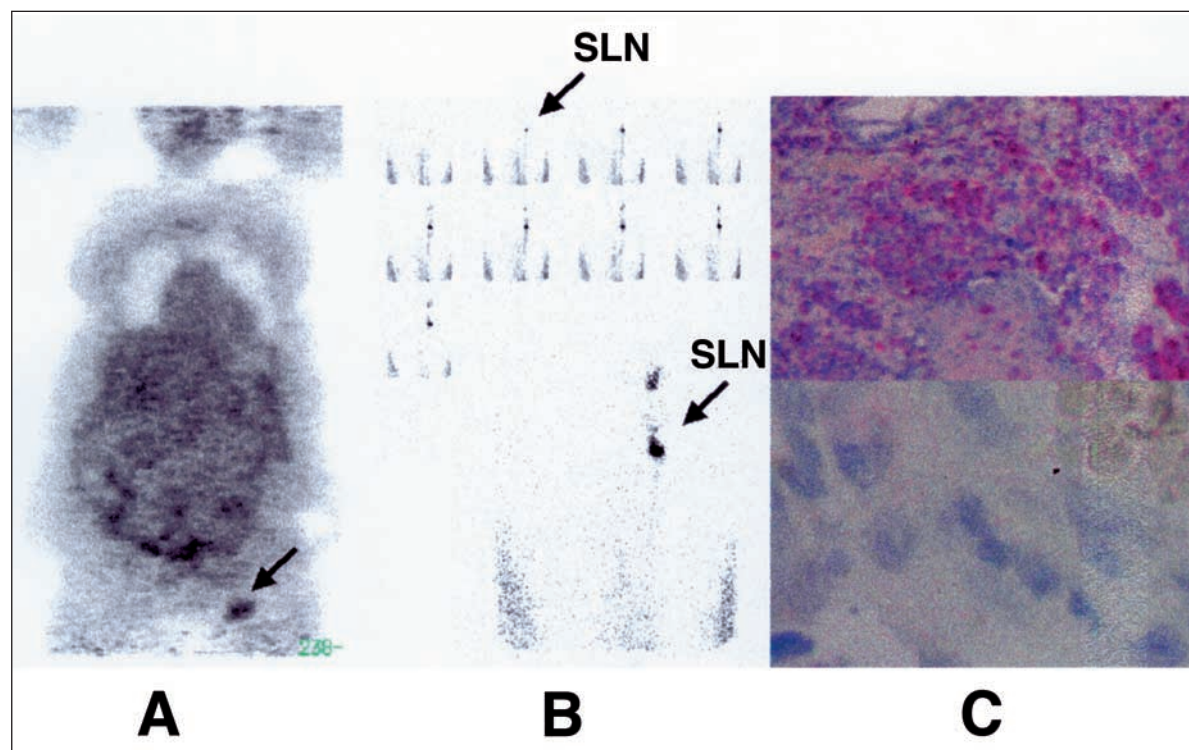


Figure 1. A case of malignant melanoma of the left foot (Breslow's depth = 4.5 mm). ^{18}F FDG PET imaging (A) accurately detected an involved sentinel node harvested at the left groin (B). Histology revealed that the sentinel node measured 1.8 cm and had massive tumor involvement with capsular infiltration (C). ^{18}F FDG PET = ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography; SLN = sentinel lymph nodes.

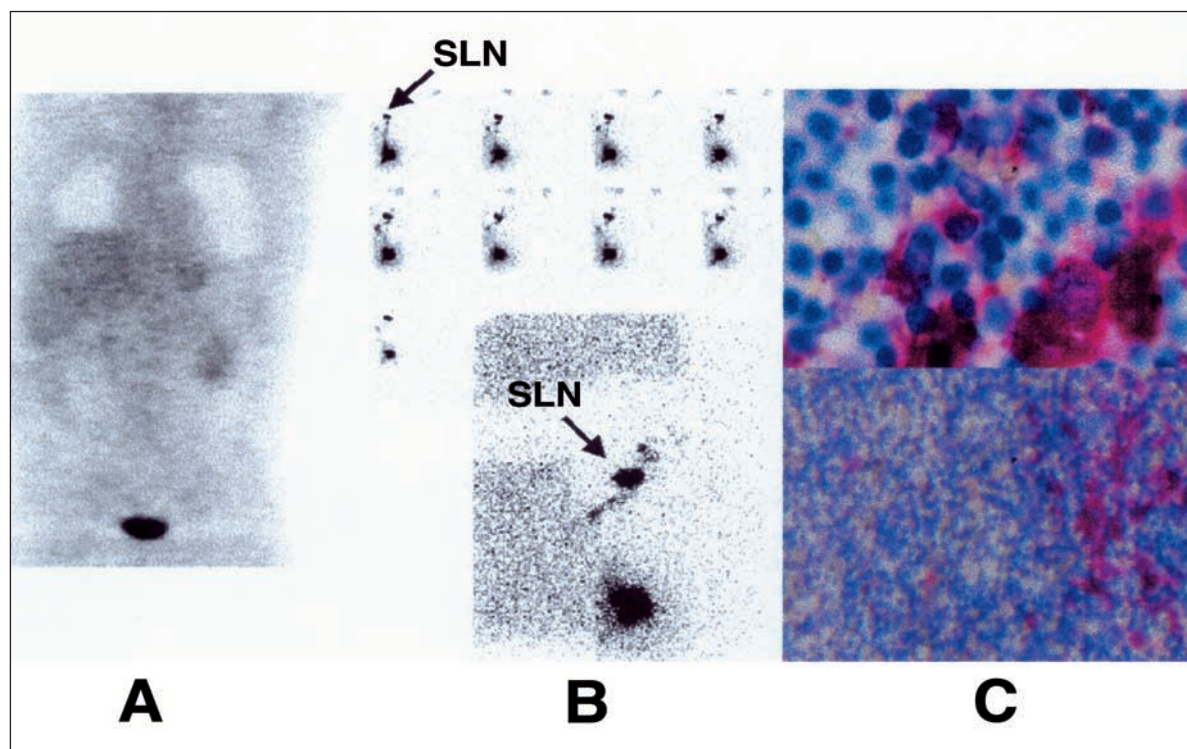


Figure 2. A case of malignant melanoma of the back (Breslow’s depth = 1.33 mm). ¹⁸F-DG PET imaging was negative (A). The sentinel node located at the right axilla was involved (B). Histology showed focal tumor deposits measuring 0.6 cm (C). ¹⁸F-DG PET = ¹⁸F-fluoro-2-deoxy-D-glucose positron emission tomography; SLN = sentinel lymph nodes.

| Table 2. Overall results | | |
|------------------------------------|--------------|----------------|
| | PET | LM/SL |
| Sensitivity (95% CI) | 14% (0-28) | 86% (72-100) |
| Specificity (95% CI) | 93% (83-103) | 100% (100-100) |
| Diagnostic accuracy (95% CI) | 67% (47-87) | 95% (86-104) |
| Positive predictive value (95% CI) | 50% (29-71) | 100% (100-100) |
| Negative predictive value (95% CI) | 68% (49-88) | 93% (83-103) |

Abbreviations: PET = positron emission tomography; LM/SL = lymphatic mapping/sentinel lymphadenectomy; CI = confidence interval.

Introduction of LM/SL in malignant melanoma was a substantial advance for the detection of subclinical nodal metastases. The technique is, nowadays, standardized and allows for the selection of a subset of patients presenting with clinically unsuspected involvement of their sentinel nodes for complete lymphadenectomy and systemic adjuvant treatments. Moreover, the procedure is useful to avoid the cost and morbidity of unnecessary elective lymph node dissections in the wide majority of the patients with an SLN free of tumor [6-10]. Owing to the determinant data provided by LM/SL in the management of patients with stage I and II melanoma, the results of this procedure recently have been incorporated into the last version of the revised AJCC staging system [25].

On the other hand, the value of ¹⁸F-DG PET for staging various malignancies is firmly established [11-14]. In pre-treatment nodal staging of malignant melanoma, however, the role of metabolic imaging is less evident. Despite the optimistic conclusions of initial reports, more recent prospective and retrospective studies are less enthusiastic about the actual performance of PET for detecting occult lymph node metastases. For instance, in 13 patients, *Gritters et al.* reported the detection of melanoma metastases in 100% of the lymph node basins [15]. Similarly, in 11 melanoma patients submitted to complete lymphadenectomy of 14 nonpalpable lymph node basins, *Wagner et al.* reported a sensitivity and a specificity of 100% for the detection of nodal metastases by means of

¹⁸F-DG PET [18]. Several other studies also confirmed the performance of ¹⁸F-DG PET for the detection of occult or residual lymph node metastases [12, 14, 16, 17, 19]. Nonetheless, only a few studies recently addressed the value of metabolic imaging for staging subclinical nodal metastases detected by the LM/SL procedure. In a prospective study of 70 patients presenting with AJCC stage I, II, or III cutaneous melanoma, *Wagner et al.* first compared PET imaging of regional lymph node basins with sentinel node biopsy results (SNB). They concluded that PET had a sensitivity of 16.7% and a specificity of 95.8% versus 94.4% and 100%, respectively, for SNB [20]. Similar observations were reported by *Acland et al.* in a prospective study of 50 patients with primary melanoma >1 cm thick or lymphatic invasion [21]. Of the 14 patients with positive SLNs, PET detected none of them. More recently, *Kokoska et al.* prospectively evaluated the value of PET and lymphoscintigraphy in the management of 18 head and neck melanoma patients [24]. Sentinel nodes were found in 94.4% of the patients, in which 5/18 (27.8%) had metastases. PET detected nodal metastases in three patients (16.7%), and only one of them had a positive SLN. In another study, *Acland et al.* retrospectively showed that the sensitivity of PET was correlated with the AJCC stage of melanoma disease [22]. They found a high sensitivity of 93% for stage III, but the value dramatically fell to 50% and 33% for stages I and II, respectively. They concluded that PET is a valuable procedure for staging the patients with known regional spread but is suboptimal in stage I or stage II disease. Similarly, in a prospective study of 95 patients, *Tyler et al.* confirmed the clinical utility of ¹⁸F-DG PET imaging in melanoma patients with AJCC stage III disease [28].

To determine the factors that may influence the sensitivity of the metabolic imaging for detecting melanoma nodal metastases, *Crippa et al.* analyzed the value of PET in terms of lymph node size [29]. In a retrospective study of 36 patients presenting with confirmed lymph node metastases from melanoma, the authors showed that PET had only a 23% sensitivity for lymph node metastases ≤ 5 mm, while the sensitivity increased to 83% and 100%, respectively, for metastases that were 6-10 mm and ≥ 10 mm. More recently, *Wagner et al.* retrospectively studied the tumor volume threshold for successful PET imaging of melanoma nodal metastases in 45 patients with 49 pathologically positive regional nodal basins [23]. The sensitivity of PET for detection of all tumor volumes was 49%. The observed 90% sensitivity threshold of nodal metastases was ≥ 78 mm³. PET sensitivity fell to 14% for detection of tumor volumes < 78 mm³. Indeed, the PET sensitivity differed by prescan AJCC stage: 0% (stage I), 24% (stage II), 81% (stage III), and 100% (stage IV).

Although these prospective and retrospective trials assessed the sensitivity of metabolic imaging for detecting

sentinel node metastases on large patient populations, they had technical biases regarding their PET protocol. For instance, a correction of attenuation and an iterative reconstruction, two key parameters affecting the quality of the images, and thus, the sensitivity of the technique, were inconsistently or never performed [30-32]. Despite the relatively limited sample size of our study group, the results were enhanced by fully corrected whole-body PET imaging, blinded PET interpretations, use of single PET examiner, and iterative data reconstruction in all cases. Indeed, the prospective nature of the study with a median follow-up time of 12 months, as well as the strict adherence to LM/SL protocol performed by the same surgical team, detailed histological analyses of SLN specimens by the same pathologist, and multidisciplinary review of all clinical cases were other important points strengthening the robustness of our conclusions. Overall, our data demonstrated the inability of PET to visualize infracentimetric sentinel node metastases in patients with early-stage melanoma. Although statistically limited, our results are similar to those published by *Wagner* and *Acland* from larger series (≥ 50 patients) [20, 21]. Both authors concluded on the inability of PET to detect microscopic metastases located in sentinel nodes. Also, our results provide additional arguments regarding the comparison of PET with sentinel node biopsy using an optimal methodology, and thus, avoiding the technical biases characterizing the available data from the literature, thereby inciting further studies with larger series to definitely confirm our conclusions. The limited spatial resolution of commercially available PET devices is certainly the main reason explaining the low sensitivity of PET for detecting microscopic lymph node metastases. Another important issue is the detector materials characterizing the PET scanners. In all published studies, the imaging was performed using Siemens ECAT line devices with bismuth germanate (BGO) detectors. We used two types of the same PET scanner (PENN PET and C-PET). Both had 6 thallium-doped sodium iodine detectors (NaI [TI]), but the curved detectors and larger axial field of view characterizing the C-PET model contribute to improve its count-rate capability and spatial resolution in comparison with the PENN PET [33, 34]. All these devices, regardless of their constructors, are representative of mid-end PET scanners commonly used in the field of oncology. Their theoretical spatial resolution is about 6 mm. In clinical practice, however, their resolution is around 1 cm and certainly more for uncorrected images. The recent introduction of lutetium oxyorthosilicate (LSO) and gadolinium oxyorthosilicate (GSO) detectors in high-end PET scanners could improve the detection efficiency [13]. Both LSO and GSO are faster than either BGO or NaI [TI], and both scintillating materials also have a higher

effective Z and density than NaI [Tl]. Future improvements in the correction of scatter fraction, as well as the implementation of more effective iterative methods for data reconstruction and the use of more powerful processing systems could also substantially increase the sensitivity and the resolution of the PET scanners [13, 35-39]. Nonetheless, we believe that the spatial resolution of these new PET systems would still be insufficient to detect 1 or 2 melanoma cells in normal-sized nodes. As demonstrated by the present study, most of the involved sentinel nodes harbored microscopic and focal tumor deposits, requiring, in two patients, sophisticated immunostaining techniques. In another case, the same-basin recurrence also showed the current limits of LM/SL and indicated the need for still more sensitive tools. For this purpose, the use of reverse transcriptase-polymerase chain reaction assay could be an efficient adjunct to detect the false negatives of both LM/SL and PET [40, 41]. Controlled trials using high-end PET with LSO or GSO detectors are, however, necessary to assess their actual performances in detecting infracentimetric nodal metastases from melanoma. Also, following evidence-based medicine methods, our results, and those reported by others, support the idea that an optimal regional nodal staging of patients with early-stage melanoma would be better achieved using

lymphatic mapping and sentinel lymphadenectomy rather than ^{18}F FDG PET imaging, thereby avoiding time-consuming and expensive unnecessary imaging procedures. Metabolic imaging remains, however, a valuable tool for whole-body staging of more advanced disease.

CONCLUSIONS

The LM/SL technique remains the procedure of choice for evaluating the histologic status of the lymphatic basins in patients with early-stage cutaneous melanoma. PET imaging appears insufficiently sensitive for localizing microscopic sentinel node metastases given its current spatial resolution. Based on our results and data from literature, we do not recommend ^{18}F FDG PET as a first-line imaging strategy for staging patients with AJCC stage I or II primary disease. Further prospective and multicentric trials, including larger series of melanoma patients and using high-end PET scanners with optimal methodology, are needed to confirm our conclusions.

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